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Osteoporosis in Men

Sundeep Khosla, Shreyasee Amin, and Eric Orwoll

Endocrine Research Unit (S.K.) and Division of Rheumatology (S.A.), College of Medicine, Mayo Clinic, Rochester, Minnesota 55905; and Division of Endocrinology (E.O.), Oregon Health & Science University, Portland, Oregon 97201

With the aging of the population, there is a growing recognition that osteoporosis and fractures in men are a significant public health problem, and both hip and vertebral fractures are associated with increased morbidity and mortality in men. Osteoporosis in men is a heterogeneous clinical entity: whereas most men experience bone loss with aging, some men develop osteoporosis at a relatively young age, often for unexplained reasons (idiopathic osteoporosis). Declining sex steroid levels and other hormonal changes likely contribute to age-related bone loss, as do impairments in osteoblast number and/or activity. Secondary causes of osteoporosis also play a significant role in pathogenesis. Although there is ongoing controversy regarding whether osteoporosis in men should be diagnosed based on female- or male-specific reference ranges (because some evidence indicates that the risk of fracture is similar in women and men for a given level of bone mineral density), a diagnosis of osteoporosis in men is generally made based on male-specific reference ranges. Treatment consists both of nonpharmacological (lifestyle factors, calcium and vitamin D supplementation) and pharmacological (most commonly bisphosphonates or PTH) approaches, with efficacy similar to that seen in women. Increasing awareness of osteoporosis in men among physicians and the lay public is critical for the prevention of fractures in our aging male population. (*Endocrine Reviews* 29: 441–464, 2008)

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Abbreviations: BV/TV, Bone volume/tissue volume; CI, Confidence interval; DHEA, dehydroepiandrosterone; Dpd, deoxypyridinoline; DXA, dual x-ray absorptiometry; HR, high resolution; IGFBP, IGF binding protein; NTx, N-telopeptide of type I collagen; PINP, amino-terminal propeptide of type I collagen; pQCT, peripheral QCT; pyr, person years at risk; QCT, quantitative computed tomography; TbN, trabecular number; TbSp, trabecular separation; TbTh, trabecular thickness; vBMD, volumetric BMD.

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I. Introduction

OSTEOPOROSIS IN MEN is not a rare problem and is an important clinical issue for men, just as it is for women. Men are estimated to lose bone mineral density (BMD) at a rate of up to 1% per year with advancing age (1, 2), and one in eight men over age 50 yr will experience an osteoporosis-related fracture in their lifetime (3). Of all osteoporotic fractures, hip fractures contribute to the greatest morbidity as well as mortality, both of which are much greater in men than in women (4–7). Almost 30% of all hip fractures occur in men (8, 9). With the increasing size of our aging population and the improving longevity of men, osteoporosis in men will soon become an even greater burden to society and health care systems worldwide. Thus, a better understanding of the epidemiology, pathogenesis, diagnosis, and treatment of osteoporosis in men will become increasingly important both to the practicing endocrinologist and the primary care provider.

II. Epidemiology of Fractures in Men

A. Overview

Fractures represent the primary clinical consequence of osteoporosis. In both men and women, osteoporosis is defined as an asymptomatic systemic bone disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility

of 75 yr, when the risk increases exponentially. Although the absolute incidence varies geographically (26), this marked increase in age-specific hip fracture incidence in elderly men is documented worldwide in population-based studies from North America (8, 27–30), South America (31, 32), Europe (11, 15, 16, 18, 20, 22, 31, 33–42), Australia (19, 43, 44), Asia (31, 45–50), and Africa (51, 52). The highest incidence for hip fracture in men was found in Scandinavian and other northern European countries, as well as in whites from North America (53, 54). On the other hand, some of the lowest incidence rates have been reported among blacks and Asians (53, 54). In more recent reports, hip fracture incidence was also observed to be low in South America and equatorial areas (26). Johnell *et al.* (55) reported a 0.3% increase ($P < 0.001$) in 10-yr probability of hip fracture risk per 10° latitude increment in men (0.8% in women). Results remained similar after adjustment for economic prosperity (55), which was also found to be associated with increased hip fracture risk (countries with greater economic prosperity having a higher risk of hip fracture) (55). The age-adjusted female to male ratio for hip fractures has been observed to be highest for whites, with a ratio up to 3–4:1 (53), but in parts of Asia and among blacks from South Africa, the female to male ratio may be closer to 1:1, with men even having a higher incidence of hip fractures than women in some reports (45, 53, 56). More recent findings from some parts of Asia, however, report a female to male ratio of 2.5, which is only slightly lower than the 2.9 ratio observed in the United States (49). Differences in trauma exposure, not just bone strength, between men and women and among men from different parts of the world may also explain some of the geographic differences observed in hip fracture rates. For example, in a study from China, where the incidence of fracture in men and women was almost equal, hip fractures in older Chinese men were more likely to be due to accidents compared with women, especially falls from bicycles (28 *vs.* 10%) (47). Genetic, environmental and lifestyle factors may all contribute to the variability in hip fracture incidence observed worldwide.

Over the past several decades, there has also been a secular increase in the age-adjusted incidence of hip fractures documented worldwide (28, 33–35, 46, 57–59), particularly in men (33, 57–59). More recently, this increase has started to level off in some areas (36–38, 41, 60, 61), although not everywhere (42, 50, 62). With the improving longevity of men and the increasing size of the population, the number of men with hip fracture worldwide is estimated to reach 1.8 million in 2050 (8), whereas others suggest that it could even reach 6.8 million, if modest assumptions regarding future secular trends are considered (63).

The mortality and morbidity associated with hip fractures are greater for men than women (4–7, 64–71). Men are twice as likely to die in hospital after a hip fracture than women (6, 7). Estimates for the 1-yr mortality rate after hip fracture ranges from 31–35% in men compared with 17–22% in women (4, 64, 65, 70). Greater number of comorbid conditions at the time of fracture contribute to mortality risk (6, 72–74), which may account for the difference observed between men and women. It has also been reported that up to 50% of men may need institutionalized care after hip fracture (7, 72), whereas among those who do return home, many are unable to regain their level of function before fracture (72). Men are less likely to return to autonomous living circumstances than women at 1 yr after hip fracture (64). In men ages 60–69 yr, the decrease in life expectancy after a hip fracture is 11.5 yr, compared with men ages 70–79 yr and age 80 yr or older, where the decrease in life expectancy is 5 and 1.5 yr, respectively (5). Despite these facts, men are less likely to be investigated or treated for osteoporosis after hip fracture (65). In one study, only 7% of men compared with 31% of women were given osteoporosis therapy of any kind at the time of hospital discharge (65). At 1 to 5 yr of follow-up, 27% of men were receiving osteoporosis treatment in contrast to 71% of women (65), whereas 67% of these men receiving treatment were only on calcium and vitamin D (65).

D. Vertebral fractures

The epidemiology of vertebral fractures is more challenging to determine because vertebral fractures are not always associated with pain that would bring them to clinical attention. Many are noted incidentally on radiographs, so the true incidence of these fractures is often underestimated. Nevertheless, even "silent" vertebral fractures, noted as vertebral deformities on radiographs, are clinically relevant because they are associated with low bone density and an increased risk for subsequent osteoporotic fracture.

The European Vertebral Osteoporosis Study (EVOS) determined the prevalence of radiographically defined vertebral deformity in 15,570 subjects (of whom 46% were men) ages 50–79 yr, from 19 countries in Europe. The age-standardized prevalence of vertebral deformity was estimated to be the same for both men and women, either 12 or 20%, depending on the criteria used to define vertebral deformity (75). However, below age 65 yr, men had a higher prevalence of vertebral deformity than women, whereas after this age, the trend was reversed (75). In both men and women, the prevalence of vertebral deformity increased with age, although the increase was greater in women after age 65 yr (75). Similar trends were noted in a U.S. study of 899 women and 529 men over age 50 yr (76), as well as in a study of thoracic spine fractures in 27,000 women and 30,000 men in Finland (77). In a study of men in the MINOS cohort, there was an age-related increase in prevalence of vertebral deformity, regardless of the definition for vertebral deformities (78). The prevalence of vertebral deformity also was noted to increase with decreasing bone density at the total hip (78).

The European Prospective Osteoporosis Study (EPOS) determined the incidence of vertebral fractures in men and women from Europe (79). A total of 14,011 men and women age 50 yr and older were recruited from population-based registers in 29 European centers, and after a mean follow-up of 3.8 yr (1.4–7.9 yr), 6788 (3174 men) had baseline and follow-up spinal radiographs (79). Vertebral fractures were defined by both morphometric criteria and qualitative assessment (79). The age-standardized incidence of morphometric vertebral fractures was 5.7 per 1000 person years at risk (pyr) in men *vs.* 10.7/1000 pyr in women (79). Using the qualitative assessment, the incidence of vertebral fracture was 6.8/1000 pyr and 12.1/1000 pyr for men and

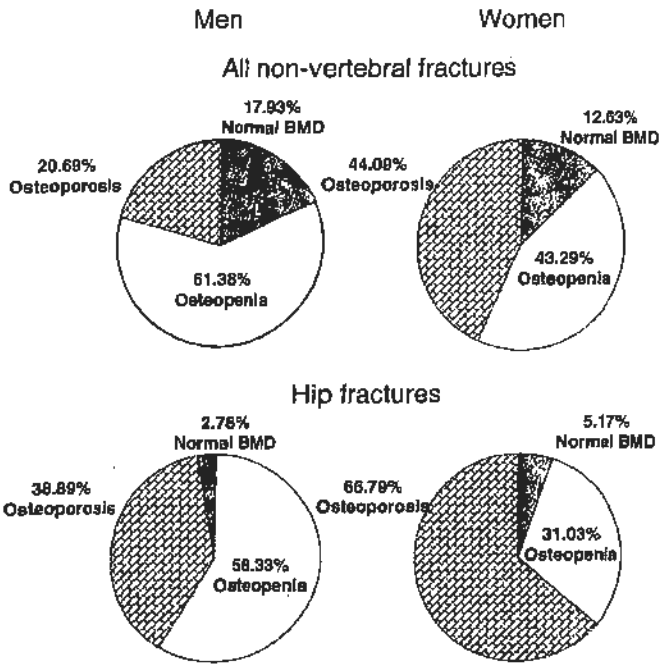

FIG. 2. Percentage of nonvertebral or hip fractures that occurred in men and women with osteoporosis, osteopenia, or normal BMD using gender-specific T-scores. [Reproduced from S. C. E. Schuit *et al.*: *Bone* 34:195–202, 2004 (20), with permission from Elsevier.]

than either Hispanic or black men (104–106). Comparative prevalence estimates in the United States among Asian populations have not been studied for men. Although Asian men do tend to have similar or slightly lower bone density values when compared with white men (107), hip fracture incidence among Asian men in the United States is actually lower than white men (104, 108). Data on prevalence estimates for osteoporosis in men from other countries are limited.

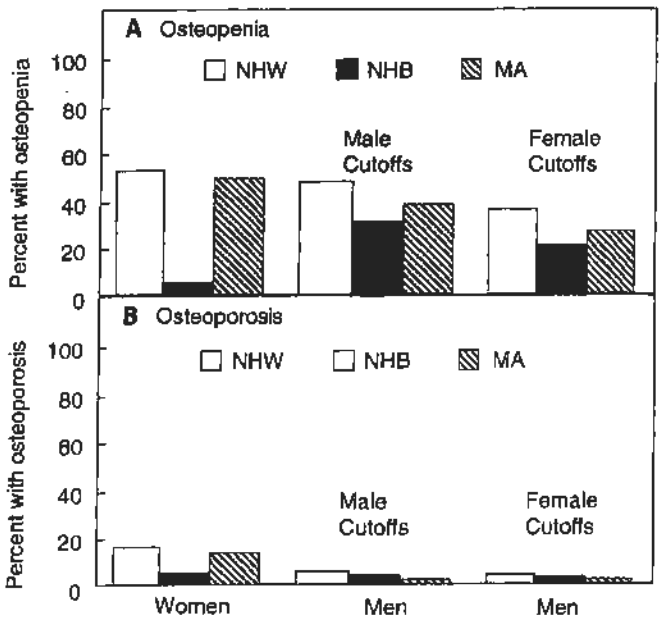

FIG. 3. Patterns of osteopenia and osteoporosis by race or ethnicity in men using either male or female cutoffs compared with the patterns seen in women. NHW, Non-Hispanic white; NHB, non-Hispanic black; MA, Mexican American. [Reproduced from A. C. Looker *et al.*: *J Bone Miner Res* 12:1761–1768, 1997 (100), with permission of the American Society for Bone and Mineral Research.]

III. Pathogenesis of Bone Loss in Men

A. Overview

Male osteoporosis is a heterogeneous entity with multiple underlying causes. Thus, although it is useful to consider each of the possible causes individually for a better understanding of pathogenesis, several different factors may be present in any given individual. Table 1 lists the major causes of bone loss in men, separating these into primary causes (age-related and idiopathic osteoporosis) and secondary causes (those due to clearly identifiable diseases or drugs). Many of these are discussed in more detail in subsequent sections, although an exhaustive discussion of each of the secondary causes of osteoporosis is beyond the scope of this review.

B. Age-related bone loss in men

1. Pattern of age-related changes in bone mass in men. Although DXA is an extremely important clinical tool, its utility is limited by the fact that it cannot clearly separate trabecular from cortical bone or provide information on possible changes in bone size or geometry with age. However, the recent application of central and peripheral quantitative

TABLE 1. Primary and secondary causes of osteoporosis in men

Primary osteoporosis
Age-related osteoporosis
Idiopathic osteoporosis
Secondary osteoporosis
Alcoholism
Glucocorticoid excess (endogenous or exogenous)
Hypogonadism (*e.g.*, hormonal suppressive therapy for prostate cancer)
Hyperparathyroidism
Hyperthyroidism
Gastrointestinal disorders
Malabsorption syndromes
Inflammatory bowel disease, gluten enteropathy
Primary biliary cirrhosis
Post gastrectomy
Hypercalciuria
Chronic obstructive pulmonary disease
Posttransplant osteoporosis
Neuromuscular disorders
Systemic illnesses
Rheumatoid arthritis
Multiple myeloma
Other malignancies
Masocytosis
Medication/drug-related
Glucocorticoids
Anticonvulsants
Thyroid hormone
Chemotherapeutics
Lifestyle choices
Cigarette smoking
Sedentary lifestyle

[Adapted from L. Gennari and J.P. Bilezikian: *Endocrinol Metab Clin North Am* 36:399–419, 2007 (29) with permission from Elsevier.]

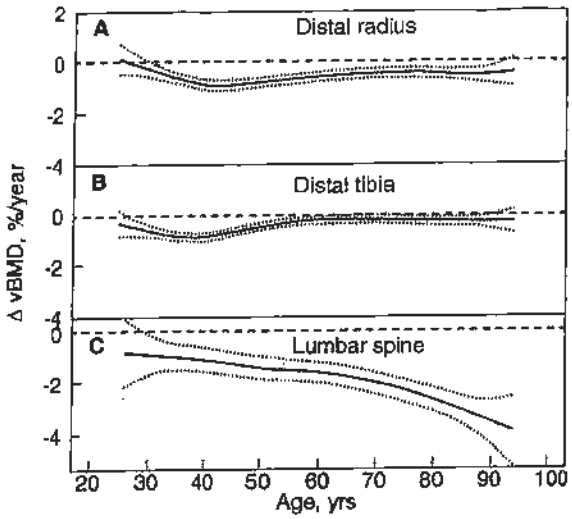

FIG. 6. Age-specific rates of change in vBMD at trabecular scanning sites in men at the distal radius (A), distal tibia (B), and lumbar spine (C). Data are shown with a smoothing spline and the 95% confidence interval. [Reproduced from B. L. Riggs *et al.*: *J Bone Miner Res* 23: 205–214, 2008 (110), with permission of the American Society for Bone and Mineral Research.]

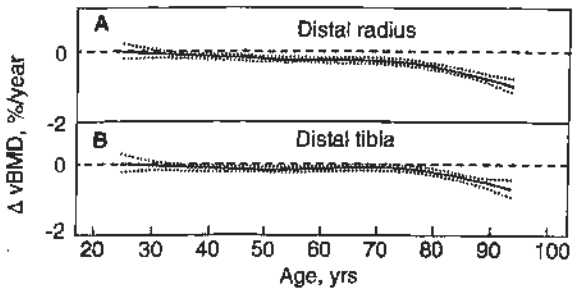

FIG. 7. Age-specific changes in vBMD at cortical scanning sites at distal radius (A) and distal tibia (B) in men. Data are shown with a smoothing spline and the 95% confidence interval. [Reproduced from B. L. Riggs *et al.*: *J Bone Miner Res* 23:205–214, 2008 (110), with permission of the American Society for Bone and Mineral Research.]

begins in young adult life, whereas cortical bone loss begins after midlife, with overall decreases in vBMD being smaller in men compared with women. There does appear to be ongoing periosteal apposition with age, with increases in bone cross-sectional area, but because of larger increases in the endocortical area, there is a net decrease in cortical area.

2. Pattern of age-related changes in bone structure in men. The development and validation of HR peripheral QCT (pQCT) imaging (112–115) has allowed for population studies of age-related changes in bone microstructure, at least at the radius and tibia. Khosla *et al.* (116) used this technology in a random sample of men (n = 278) and women (n = 324), ages 21–97 yr, to define sex and age effects on bone microstructure at the wrist. Relative to young women (ages 20–29 yr), young men had greater trabecular bone volume/tissue volume (BV/TV; by 26%, $P = 0.001$) and trabecular thickness (TbTh; by 28%, $P < 0.001$) but similar values for trabecular number (TbN) and trabecular separation (TbSp). Between ages 20 and 90 yr, cross-sectional decreases in BV/TV were similar in men (−26%) and in women (−27%) (Fig. 8A), but whereas women had significant decreases in TbN (−13%) and increases in TbSp (+24%), these parameters had little net change over life in men (+7% and −2% for TbN and TbSp, respectively; $P < 0.001$ *vs.* women; Fig. 8, B and D). However, TbTh decreased to a greater extent in men (−24%) than in women (−18%; $P = 0.010$ *vs.* men; Fig. 8C). These findings using HR-pQCT imaging are, in fact, very similar to earlier studies by Aaron *et al.* (117) using cadaveric transiliac bone biopsies. These investigators also found parallel decreases in BV/TV with age in men and women, as well as a significant decrease in TbN over life in women but not in men. In addition, similar to the HR-pQCT data, TbTh at the iliac crest was higher in young men compared with age-matched women, but decreased more over life in men compared with women (117). The concordance of age-related changes in trabecular structure at the radius using HR-pQCT with the previous work using bone histomorphometry does suggest that the pattern of changes in trabecular bone may be similar at multiple skeletal sites. Collectively, these data indicate that whereas decreases with age in trabecular BV/TV are similar in men and women, the structural basis for the decrease in trabecular volume is quite different between the sexes. Thus, over life, women undergo loss of trabeculae with an increase in TbSp, whereas men begin young adult life with thicker trabeculae and primarily sustain trabecular thinning, with no net change in TbN or TbSp. Because decreases in TbN have been shown by finite element modeling (118) to have a much greater impact on bone strength compared with decreases in TbTh, these findings may help explain the lower lifelong risk of fractures in men, and specifically, their virtual immunity to age-related increases in distal forearm fractures.

3. Role of sex steroids. Because most men do not develop overt hypogonadism with aging, the prevailing opinion had been that sex steroid deficiency was not a major cause of age-related bone loss in men. It is now clear, however, that the failure of earlier studies to find major decreases in serum levels of total sex steroids was caused by the fact that they did not account for the confounding effect of a greater than 2-fold age-related rise in levels of serum SHBG (119). It is generally believed that circulating sex steroids that are bound to SHBG have restricted access to target tissues, whereas the 1 to 3% fraction that is free and the 35 to 55% fraction that is bound loosely to albumin are readily accessible (120, 121). Although there are various methods to assess the bioavailable, or non-SHBG-bound, sex steroids, several groups have reported substantial decreases in serum levels of free or bioavailable sex steroid levels with aging (119, 122). Data from a population of 346 men from Rochester, Minnesota (119), are shown in Table 2. Similar findings were reported by Orwoll *et al.* (123) from the MrOs study, where in a sample of 2623 men over the age of 65 yr, serum free testosterone and free estradiol declined significantly with age, and this was associated with increases in serum SHBG levels. The precise cause of the age-related increase in serum SHBG levels and the failure of the hypothalamic-pituitary-testicular axis to compensate for this and maintain free or

those subjects with serum free estradiol levels below the median value lost bone over 4 yr at the lumbar spine and femur neck, whereas the men with free estradiol levels above the median did not lose bone. In further studies using QCT at various sites, Khosla *et al.* (132) found that in elderly men, bioavailable estradiol was the most consistent predictor of vBMD and some of the geometric variables related to bone size, and that the possible "threshold" for skeletal estrogen deficiency was most evident at cortical sites. Moreover, at least in men, serum estradiol levels measured by either a sensitive RIA or by tandem mass spectroscopy provided virtually identical correlations with BMD (133).

Because 85% or more of circulating estrogen levels in men are derived not from direct testicular secretion but rather from peripheral aromatization of testosterone (134), several studies have examined possible relationships between variations in the enzyme aromatase (CYP19) that is responsible for the conversion of androgens to estrogens in the testis and in peripheral tissues and BMD in men (135, 136). Thus, Gennari *et al.* (136) found that males with a high number of TTAA repeat sequences in intron 4 of the CYP19 gene had higher serum estradiol levels and decreased rates of bone loss compared with those with a lower number of repeats, irrespective of serum SHBG or androgen levels. Interestingly, the association between the CYP19 polymorphisms and serum estradiol levels was attenuated with increases in fat mass, consistent with a role for peripheral adipose tissue in contributing to circulating estrogen levels in men and in reducing the impact of genetic variation in the CYP19 enzyme by simply increasing the amount of enzyme present peripherally.

Although these studies helped to establish that estrogen levels are associated with skeletal maintenance in males, they could not definitively establish causal relationships. To address this issue, Falahati-Nini *et al.* (137) performed a direct interventional study to distinguish between the relative contributions of estrogen *vs.* testosterone in regulating bone resorption and formation in normal elderly men. Endogenous estrogen and testosterone production were suppressed in 59 elderly men using a combination of a long-acting GnRH agonist and an aromatase inhibitor. Physiological estrogen and testosterone levels were maintained by simultaneously placing the men on estrogen and testosterone patches delivering doses of sex steroids that mimicked circulating estradiol and testosterone levels in this age group. After baseline measurements of bone resorption [urinary deoxypyridinoline (Dpd) and N-telopeptide of type I collagen (NTx)] and bone formation [serum osteocalcin and amino-terminal propeptide of type I collagen (PINP)] markers, the subjects were randomized to one of four groups: group A (−T, −E), discontinued both the testosterone and estrogen patches; group B (−T, +E), discontinued the testosterone patch but continued the estrogen patch; group C (+T, −E), continued the testosterone patch but discontinued the estrogen patch; and group D (+T, +E) continued both patches. Because gonadal and aromatase blockade was continued throughout the 3-wk period, separate effects of estrogen *vs.* testosterone (in the absence of aromatization to estrogen) on bone metabolism could be delineated.

As shown in Fig. 9A, significant increases in both urinary Dpd and NTx excretion, group A (−T, −E), were prevented completely by continuing testosterone and estrogen replacement [group D (+T, +E)]. Estrogen alone (group B) was almost completely able to prevent the increase in bone resorption, whereas testosterone alone (group C) was much less effective. Using a two-factor ANOVA model, the effects of estrogen on urinary Dpd and NTx excretion were highly significant ($P = 0.005$ and 0.0002, respectively). Estrogen accounted for 70% or more of the total effect of sex steroids on bone resorption in these older men, whereas testosterone could account for no more than 30% of the effect. Using a somewhat different design, Leder *et al.* (138) have confirmed an independent effect of testosterone on bone resorption, although the data in the aggregate clearly favor a more prominent effect of estrogen on the control of bone resorption in men.

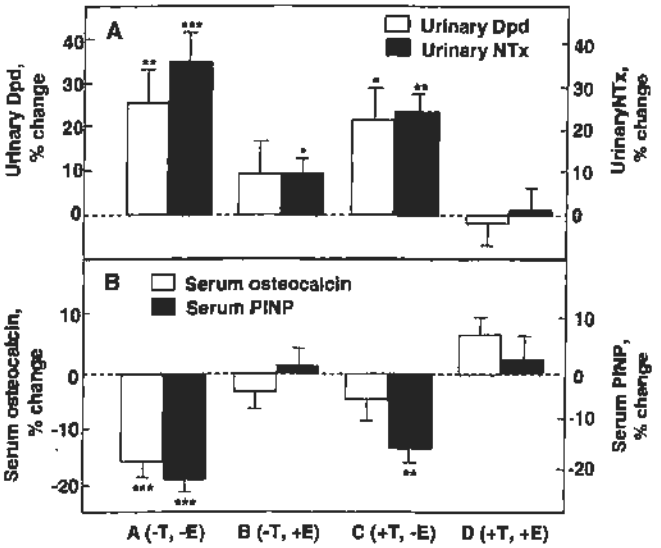

FIG. 9. Percent changes in bone resorption markers (urinary Dpd and NTx) (A) and bone formation markers [serum osteocalcin and N-terminal extension peptide of type I collagen (PINP)] (B) in a group of elderly men (mean age 68 yr) made acutely hypogonadal and treated with an aromatase inhibitor (group A), estrogen alone (group B), testosterone alone (group C), or both (group D). See text for details. *Asterisks* indicate significance for change from baseline: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. [Adapted from A. Falahati-Nini *et al.*: *J Clin Invest* 106:1553–1560, 2000 (137), with permission from the American Society of Clinical Investigation.]

Figure 9B shows the corresponding changes in the bone formation markers, serum osteocalcin and PINP. The reductions in both osteocalcin and PINP levels with the induction of sex steroid deficiency (group A) were prevented with continued estrogen and testosterone replacement (group D). Interestingly, serum osteocalcin, which is a marker of function of the mature osteoblast and osteocyte (139), was maintained by either estrogen or testosterone (ANOVA P values of 0.002 and 0.013, respectively). By contrast, serum PINP, which represents type I collagen synthesis throughout the various stages of osteoblast differentiation (140), was maintained by estrogen (ANOVA P value 0.0001), but not testosterone.

Collectively, these findings provided conclusive proof of an important (and indeed, dominant) role for estrogen in

explain, at least in part, the age-related increase in circulating SHBG levels (119). Thus, IGF-I has been shown to inhibit SHBG production by hepatocytes *in vitro* (168), and serum SHBG levels are inversely correlated with IGF-I levels in men (169). As such, age-related changes in the GH/IGF system may modulate the activity of sex steroids via changes in circulating SHBG levels.

Other changes in endocrine function with aging appear to make smaller contributions to bone loss. Among the weak adrenal androgens, levels of serum dehydroepiandrosterone (DHEA) and DHEA sulfate decrease by about 80% (170), but the role of these changes in mediating bone loss is unclear. In a recent clinical trial, Nair *et al.* (171) found small (~2%) increases in BMD at the femur neck, but not other skeletal sites, after 2 yr of DHEA treatment of elderly men, arguing against an important role for DHEA in age-related bone loss in men.

Finally, whereas the above discussion has focused on age-related changes in hormonal or other growth factors, it is also likely that with aging, there are intrinsic changes in stem or osteoprogenitor cells that result in impairments in bone formation. However, possible changes in these cells with aging have not been clearly defined, and this is an important area for future investigation.

5. Role of other factors, including nutrition and changes in muscle mass. As noted above, vitamin D deficiency, with or without adequate calcium intake, likely contributes to the age-related increase in serum PTH levels and to bone loss, at least in a subset of aging men (160). In several population-based studies, 25-hydroxyvitamin D, an indicator of vitamin D nutrition, decreased by 30–60% (172). This may be a particularly important problem in housebound individuals with poor nutrition and inadequate exposure to UV radiation, especially populations who reside in countries with higher latitudes, such as Great Britain and France, and where dairy products are not fortified with vitamin D. Other nutritional factors, such as inadequate calcium (173) or protein (174) intake may also play a role in accelerating age-related bone loss in men. In addition to these nutritional factors, Frost has suggested in a number of publications (175–177) that the loss of muscle mass with aging is perhaps the principal cause of involutional osteoporosis in both sexes. Indeed, a number of studies have shown high correlations between lean body mass and total body bone mineral (177). Moreover, in a population sample, Proctor *et al.* (178) found that physical activity declined by 34 and 38% and lean body mass declined by 18 and 17% with aging in women and men, respectively, and decreases in muscle strength have been associated with the risk of osteoporosis in women as well as men (173). Thus, it appears likely that with aging, a number of nutritional and lifestyle factors, particularly declining levels of physical activity and muscle mass, contribute to bone loss as well as risk of falls, ultimately increasing the overall risk of fractures.

C. Idiopathic osteoporosis in men

For the purposes of this discussion, idiopathic osteoporosis in men is defined as the development of osteoporosis and fractures in a male before the age of 60 yr (*i.e.*, generally before the above age-related changes are evident). However, there may well be considerable heterogeneity in the causes of idiopathic osteoporosis in men. Some cases may represent mild, unrecognized variants of osteogenesis imperfecta; others may represent defects in peak bone mass acquisition caused by genetic or environmental factors. A subset of these men appear to have hypercalciuria with or without increased bone resorption (179–181). Indeed, idiopathic hypercalciuria in men is associated with low BMD (179), and up to 10% of men with idiopathic osteoporosis have hypercalciuria (182). Despite this heterogeneity in causes of idiopathic osteoporosis, however, there are some interesting similarities to the hormonal abnormalities being uncovered in these patients and those present in elderly men.

Perhaps the most consistent abnormality noted in the albeit small groups of patients studied to date in an increase in serum SHBG levels, leading to decreased free estradiol and androgen indices (183–186). Circulating total estradiol levels may also be reduced in these patients despite normal testosterone levels, consistent with subtle aromatization defects in at least a subset of these patients (183, 187). Interestingly, circulating IGF-I levels may also be reduced in these patients (188), despite a normal GH secretory capacity (189). The reduction in IGF-I levels appears to be associated with a simple sequence repeat in the IGF-I gene (192/192) that is present at an increased frequency in these men (190). As with aging, low IGF-I levels may contribute both to impaired bone formation and to an increase in SHBG levels, the latter resulting in reduced availability of sex steroids. Thus, there are some striking parallels in the hormonal abnormalities present in these younger men with idiopathic osteoporosis and those present in aging men that clearly warrant further investigation.

D. Secondary osteoporosis in men

As shown in Table 1, there are a number of possible secondary causes of osteoporosis in men that may be superimposed on underlying age-related bone loss or idiopathic osteoporosis. Indeed, in some series, secondary causes may account for, or contribute significantly to, up to 40% of the cases of osteoporosis in men (191). The three major causes of secondary osteoporosis in men are alcohol abuse, glucocorticoid excess (either endogenous or, more commonly, chronic glucocorticoid therapy), and overt hypogonadism, with the latter increasingly due to hormonal suppressive therapy for the treatment of prostate cancer (192). Of these, glucocorticoid-induced osteoporosis is the most common cause of secondary osteoporosis in men; however, because this disorder is not unique to men, it is not discussed in detail here, but the reader is referred to excellent recent discussions of this topic (193, 194). The other secondary causes listed in Table 1 should be considered and ruled out in the appropriate clinical setting, but a detailed discussion of each of these is beyond the scope of the present discussion.

IV. Diagnostic Criteria

A. Overview

Unfortunately, guidelines for efficient, cost-effective evaluations of patients having, or suspected of having, osteopo-

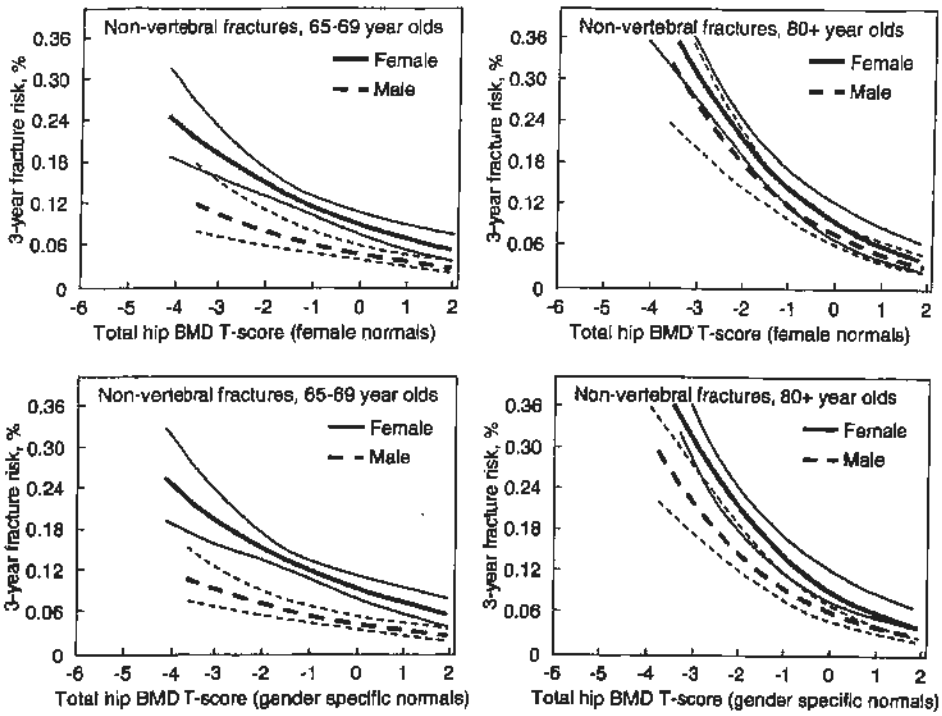

FIG. 11. Three-year risk of fracture (and 95% confidence limits) by sex-specific total hip BMD T-score and age in older women and men. T-scores for males using male normal values for the total hip are equivalent to the following BMD values: T-score of -2 = 0.753 g/cm^2; T-score of -1 = 0.897 g/cm^2; T-score of 0 = 1.041 g/cm^2. T-scores for females using female normal values for the total hip are equivalent to the following BMD values: T-score of -2 = 0.698 g/cm^2; T-score of -1 = 0.820 g/cm^2; T-score of 0 = 0.942 g/cm^2. T-scores for both sexes using female normal values for the total hip are equivalent to the following BMD values: T-score of -2 = 0.698 g/cm^2; T-score of -1 = 0.820 g/cm^2; T-score of 0 = 0.942 g/cm^2. [Reproduced from S. R. Cummings *et al.*: *J Bone Miner Res* 21:1550–1556, 2006 (202), with permission of the American Society for Bone and Mineral Research.]

measures and fracture risk to substantiate the use of CT measures in men in the clinical setting.

The bone density criteria that should be used to identify men with high fracture risk, and thus in need of intervention, is controversial. Although it is clear that there is an inverse association between DXA BMD and fracture risk, the specifics of the relationship are not as well established in men as in women. Some have suggested that the relationship between the absolute level of bone density and fracture risk is the same in men and women (206), whereas others have noted sex differences (Fig. 11) (202). Interestingly, in the latter studies sex differences were most apparent at younger ages and became less apparent in older men. If true, this offers a potential explanation for the lack of sex differences in studies of hip fractures, which usually occur late in life (206). In addition to these issues, some have been concerned that the use of diagnostic cutoffs in men that are based on reference ranges in women would reduce the number of men identified as at risk (207), a conundrum in view of the frequency of fractures in men. In the absence of well-powered prospective studies involving both sexes, it remains most common to judge BMD results in light of sex-specific reference ranges. Certainly it would be preferable to utilize diagnostic criteria based on absolute fracture risk, a goal being currently addressed by several professional organizations, and models incorporating clinical risk factors with or without BMD to predict 10-yr probabilities of hip or other major osteoporotic fractures in women and men have recently been published (208). Currently, however, T-score-based criteria remain the basis for therapeutic decisions in both sexes. The diagnosis of osteoporosis in men is commonly made at a BMD T-score level of -2.5 or less, but in fact there is no obvious T-score that should dictate clinical decisions about additional evaluation or therapy. Rather, with lower levels of BMD, the clinical concern should be greater. For instance, in men with BMD T-score levels of -1.5 or less, the presence of other risk factors for fracture may trigger additional diagnostic measures or therapeutic intervention. BMD T-score levels below -2 to -2.5 commonly prompt the consideration of pharmacological therapy. Unfortunately, there are no large-scale therapeutic trials in men that allow estimates of the cost effectiveness of treatment based on baseline BMD levels.

D. Laboratory evaluation

The diagnostic yield and cost effectiveness of laboratory studies in men with low bone density is unknown. Nevertheless, in the presence of low BMD it is considered important to determine the cause of the osteopenic disorder. Of particular concern, osteomalacia is estimated to be present in <4% to 47% of men with femoral fractures, with most reports being ≤20% (209, 210). Although the exact magnitude of the problem presented by osteomalacia in men is uncertain, the differential diagnosis of low bone mass and fractures in men must include osteomalacia. This becomes particularly imperative because the treatment for osteomalacia differs considerably from that of osteoporosis.

The history and physical examination can provide evidence of genetic, nutritional/environmental, social, medical, or pharmacological factors that contribute to the cause of osteoporosis. Routine laboratory testing should include levels of serum creatinine, calcium, phosphorus, alkaline phosphatase, and liver function tests, as well as a complete blood count. Given the widespread prevalence of vitamin D deficiency (160), serum 25-hydroxyvitamin D levels should also be obtained in patients with primary or secondary male osteoporosis. However, given the potential variability of assays for 25-hydroxyvitamin D levels (211), use of a validated

tiveness of intranasal calcitonin in men include one open-label study (239) that suggested that therapy reduced the risk of vertebral fracture.

E. Thiazide diuretics

Thiazide administration may have positive effects on bone mass, rates of bone loss, and hip fracture risk in men (240, 241). For instance, in case-controlled trials the use of thiazides reduced the rate of loss in calcaneal bone density by 49% compared with controls, and the relative risk of hip fracture was halved by exposure to thiazides for more than 6 yr (242). Similarly, thiazide use in men was associated with an adjusted odds ratio of femur fracture of 0.2 (95% CI, 0.1–0.7) (243). Other diuretics did not seem to impart the same benefits. Unfortunately, none of the available studies has been randomized or controlled, so a confident estimate of the magnitude of the protective effect is not possible. The mechanism for the positive effect is unclear, but it has been postulated to stem from the hypocalciuric effects of thiazides. In fact, one study showed that an increase in BMD resulted from thiazide use in men with hypercalciuria (244). Although not appropriately considered a primary treatment modality, a thiazide is probably the diuretic of choice in osteoporotic patients (other considerations notwithstanding).

F. Strontium ranelate

Strontium ranelate administration has interesting effects on bone remodeling in that it appears to induce an increase in bone formation as well as a reduction in bone resorption and results in improved BMD and reduced fracture risk in women (245). The effects of strontium should not be sex specific, and studies of the usefulness of strontium therapy in men are under way but results are not yet available.

G. Sex steroid therapy

1. Overview. As reviewed in *Section III*, sex steroids exert complex effects on bone. Whereas there may be treatment opportunities with both estrogens and androgens, there is very little information concerning the effects of estrogens in the therapeutic context, and most treatment trials for low BMD have involved testosterone.

2. Estrogen. Although estrogens exert important effects on bone remodeling, there have been few attempts to use estrogen administration to prevent or improve bone mass in men. There is an appropriate reluctance to induce adverse effects (*e.g.*, gynecomastia), and studies of the effects of even low-dose estrogen on bone in men are not available. Two small, short-term trials of raloxifene in older men with low BMD suggested that selective estrogen receptor modulators could have positive effects on bone remodeling (246, 247), at least in the subset of men with low endogenous estrogen levels. Of course, treatment with testosterone also results in an increase in estrogen levels via the effects of aromatase, and the effects of testosterone therapy on bone are probably at least in part the result of estrogen action.

3. Testosterone replacement in hypogonadal adult men. Hypogonadism is associated with increased bone loss and fracture. Testosterone therapy in hypogonadal men positively affects bone mass, at least in most patient groups (248). The increase in bone mass with testosterone therapy can be expected to be modest in the short term (up to 24 months), but Behre *et al.* (249) noted an increase in spinal trabecular BMD of more than 20% in the first year of testosterone therapy in a group of hypogonadal men and further increases thereafter. The most marked increases were observed in those with the lowest testosterone levels before therapy. Using micro-MRI imaging, Benito *et al.* (250) noted that trabecular architecture appeared to improve in hypogonadal men treated with testosterone. Most studies of testosterone replacement have included younger men, but there is a suggestion that in older men with hypogonadism the response to therapy can be expected to be similar to that in younger adult patients (249, 251).

Despite the generally positive tenor of most studies of the skeletal effects of testosterone replacement, in some patient groups, for instance those with Kleinfelter's syndrome, the advantage associated with androgen therapy is questionable because the available studies report very mixed results (252). This may be because the level of androgen deficiency in Kleinfelter's (as in the case of some other causes of hypogonadism) is quite variable. These findings suggest the need to carefully consider the potential benefits of androgen replacement in each patient individually.

In addition to the generally positive effects of androgen replacement therapy on BMD in hypogonadal men, additional benefits may be gained from the increases that have been noted in strength and lean body mass in these patients (253). Because lean body mass and strength have been correlated with bone mass and a reduced propensity to fall, they may further serve to promote bone health and reduce fracture risk. However, thus far therapeutic trials of testosterone have included BMD as the primary endpoint, and the effects of testosterone therapy on fracture risk are unknown.

The most efficacious doses and routes of androgen administration for the prevention/therapy of bone loss in men remain uncertain. The specific testosterone levels necessary for an optimal effect have not been defined. Current recommendations are to attempt to achieve testosterone concentrations similar to those of normal young men.

4. Testosterone replacement in andropause. There is considerable controversy concerning the use of testosterone replacement therapy in older men, including its usefulness and safety in men at risk for fracture. The Institute of Medicine recommended a series of clinical trials to help determine the efficacy of testosterone for several important outcomes (254). Those trials are being developed and should provide additional information concerning bone. Although available data are few, trials of im testosterone administration in older men with low testosterone levels have suggested that it may result in increased strength and improved body composition (253) and that bone mass and biochemical indices of remodeling may improve (255). Thus far, positive effects on bone density are more apparent in men treated with im testosterone than with transdermal administration (171, 256), suggesting that higher testosterone levels may be necessary to achieve these results. Trials to date have selected men who have relatively

(273). In addition, inactivity is associated with bone loss, and exercise may aid in maintaining bone mass. Specific exercise prescriptions to accomplish these goals have not been confirmed in men or women, although strength can be dramatically increased and risk of falls reduced in the elderly with achievable levels of exercise (274). That fracture rates are lower in elderly men who exercise modestly buttresses this contention (275). Falls and fall prevention strategies have been reviewed (276, 277).

VI. Unresolved Issues Concerning Osteoporosis in Men

As is evident from this review, considerable inroads have been made into understanding all aspects of osteoporosis in men. However, there are major unresolved issues that should set the agenda for future research in this area. These include:

- The most appropriate definition for osteoporosis in men in the absence of fractures— specifically, whether male or female reference ranges should be used to define T-scores in men.
- Based on this definition, a better understanding of the true prevalence of osteoporosis in men in various ethnic groups.
- Further understanding of the hormonal and nonhormonal factors causing age-related bone loss in men and specifically, the underlying mechanism(s) for the significant, ongoing trabecular bone loss in men (and women) in young adult life.
- Further clarification of the different causes of "idiopathic" osteoporosis in young adult men, which is clearly a heterogeneous entity.
- The cost effectiveness of obtaining various laboratory tests in the evaluation of men with osteoporosis.
- The potential utility of measuring serum estradiol levels (in addition to serum testosterone levels) using standardized mass spectroscopy assays as part of the evaluation of osteoporosis in men.
- The skeletal (and nonskeletal) benefits *vs.* risks of testosterone treatment of aging men with declining total and bioavailable testosterone levels.
- Studies with pharmacological agents directly assessing fracture risk reduction in men, rather than relying on inferences from studies in women.

VII. Summary and Conclusions

With the aging of the population, osteoporosis in men is increasing as a public health problem. Hip, vertebral, and other fractures occur in men at a significant frequency, and both hip and vertebral fractures are associated with increased mortality in men. Although osteoporosis in men is a heterogeneous clinical entity, declining sex steroid levels and, in particular, declining bioavailable estradiol levels, appear to play an important role in mediating age-related bone loss in men. Other hormonal factors, such as age-related increases in serum PTH levels, vitamin D insufficiency, and declining IGF-I levels, may also have a role in pathogenesis. Secondary causes of osteoporosis also contribute significantly to fractures in men. Although there is ongoing debate regarding diagnostic criteria for defining osteoporosis in men, sex-specific reference ranges for BMD by DXA are commonly used. Fortunately, most of the drugs evaluated for the prevention and treatment of osteoporosis in women, particularly bisphosphonates and PTH, also appear to be effective in men. Given the availability of effective therapies for the prevention and treatment of osteoporosis in men, awareness regarding this disorder is critical for the prevention of morbidity and mortality as a consequence of fractures in aging men.

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Address all correspondence and requests for reprints to: Sundeep Khosla, M.D., Guggenheim 7, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905; khosla.sundeep@mayo.edu.

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